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The sole outstanding issue concerns the rejection of claims 1, 9, 10, and 17-19 under 35 U.S.C. § 103(a) as purportedly obvious based on Zara et al. (GB 2 262 526). Applicants again respectfully traverse this rejection.

The Advisory Action asserts that Table 3 in Zara shows that hydrogen was clearly contemplated as a preferred choice. Applicants respectfully disagree. While Table 3 shows numerous chemical compounds wherein R1=H, none of the exemplified compounds of Table 3, which use H at the R1 position, are a pyridazinone which resemble the pyridazinone of the claimed invention. Furthermore, those of ordinary skill in the art at the time of the invention recognized that if R1 were a hydrogen there would be a high probability of self-alkylation reaction which results in the formation of unwanted derivatives. As stated in previous Responses, Zara only contains one example for making 4-(ω-chloro-alkylamino)-pyridazone-2-one derivatives. Moreover, in the reaction shown in example 41, the N-2 nitrogen of the pyridazinone ring bears a methyl substituent and thus is protected against alkylation reactions. Hence, there is no suggestion in Zara to use a pyridazinone ring wherein the N-2 nitrogen bears a hydrogen to make the pyridazinone of the present invention.

The Advisory Action further asserts that there is no evidence of unexpected results of record. In response, Applicants submit herewith a 132 declaration of Dr. Barkoczy. Attached to the declaration are the results of a comparative experiment that was carried out to determine differences between the present invention and the method described by the Zara document. As explained in the declaration, Attachment A contains the results of a HPLC-MS analysis of the product obtained by the process described by the Zara document. Attachment B contains the results of a HPLC-MS analysis of the product obtained by the process of the present invention.

As discussed in previous Amendments, the process of the present invention differs from the process of Zara in that Zara employs a pyridazinone derivative substituted on the N atom in position 2 by a methyl group. In contrast, the present process employs a pyridazinone derivative wherein the nitrogen atom is unsubstituted.

For a comparative test, a comparative method as described by Example 41 of the Zara document was used to produce the pyridazinone derivative of Formula I of the present invention (see Attach. A). The comparative method involved melting 1.99 g of 4-(3-bromo-propylamino)-5-chloro-2H-pyradazine-3-one and 1.22 g of N-methyl-homoveratrum in a 50 ml round-bottomed flask under heating in an oil bath having a temperature of 120° C. The melt reaction mixture was stirred at this temperature for 5 hours and cooled to room temperature. 20 ml water were then added and the mixture was extracted three times with 20 ml of ethyl acetate each. The united organic layers were dried over magnesium sulfate and evaporated *in vacuo*. This resulted in 3.1 g of an oily residue.

As an example of the present invention, a product was obtained using the process of the present invention (see Attach. B).

As shown in Attach. A, according to HPLC analysis, the product which resulted from the Zara method contained 84.7% of the desired 5-chloro-4-(3-{[2-(3,4-dimethoxy-phenyl)-ethyl]-methylamino}-propylamino)-2H-pyridazinone-3-one and 3.7% of a dimer contamination corresponding to the formula 5-chloro-2-[3-(5-chloro-3-oxo-2,3-dihydro-pyridazine-4-yl-amino)-propyl]-4-(3-{[2-(3,4-dimethoxy-phenyl)-ethyl]-methylamino}-propylamino)-2H-pyridazine-3-one. In addition, to the above contaminant, further impurities were also formed in a significant amount which are not formed in the process of the present invention. Furthermore, the oily product resulting from the method of Zara cannot be further purified by

crystallization. The product resulting from the method of Zara can only be purified by chromatographical methods which are unsuitable for industrial scale production. In contrast, according to the present invention, the product obtained from the method of the present invention contains 99.78% of the desired compound and an insignificant amount (0.05%) of the undesired dimer. Accordingly, the process of the present invention enables the preparation of the desired compound at a purity which complies with the requirements of the Pharmacopoeia, even on an industrial scale.

As shown by the comparative data in the declaration, the Zara process is completely different from the present invention. The method described by the Zara document fails to yield a product that has the superior and unexpected properties of the product yielded by the inventive method with respect to product purity as demonstrated by the attached results of the side-by-side comparison. Hence, the declaration and above remarks overcome this rejection and its withdrawal is respectfully requested.

* * *

Applicants respectfully submit that this Request for Reconsideration and the above remarks obviate the outstanding rejection in this case, thereby placing the application in condition for immediate allowance. Allowance of this application is earnestly solicited.

If any fees under 37 C.F.R. §§1.16 or 1.17 are due in this filing, please charge the fees to Deposit Account No. 02−4300; Order No. 032340.004.

If an extension of time under 37 C.F.R. §1.136 is necessary and not included herewith, such an extension is requested. The extension fee should be charged to Deposit Account No. 02–4300; Order No. 032340.004.

Respectfully submitted,

SMITH, GAMBRELL & RUSSELL, LLP

By: Reg. No. 48,119
Robert G. Weilacher, Reg. No. 20,531
1850 M Street, N.W., Suite 800
Washington, D.C. 20036
Telephone: (202) 263-4300
Facsimile: (202) 263-4329

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